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Drug development for the CNS using imaging

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A basic problem in the discovery and development of novel drugs to be used in the therapy of neurological and psychiatric disorders is the absence of relevant in vitro or in vivo animal models that can yield results to be extrapolated to man. Drug research now benefits from the fast development of functional imaging techniques such as positron emission tomography (PET) which trace radiolabeled molecules directly in the human brain. PET uses molecules which are labeled with short-lived radionuclides and injected intravenously into experimental animals, human volunteers or patients. The most frequent approach is to study how an unlabelled drug inhibits specific binding of a well characterized selective PET radioligand. The alternative direct approach is to radiolabel a new potential drug and to trace its uptake, anatomical distribution and binding in brain. Furthermore, the effects of a novel drug on physiological-biochemical parameters, such as glucose metabolism or blood flow, can also be assessed. The demonstration of quantitative relationships between drug binding in vivo and drug effects in patients is used to validate targets for drug action, to correlate pharmacological and physiological effects, and to optimize clinical treatment.

The development of new drugs includes extensive pre-clinical characterization and safety documentation followed by a time-consuming search for appropriate clinical dose levels. Drug development is a time consuming and costly procedure: The molecule-to-drug-time is, on the average, about 12 years, whereas an investment of more than 500 million Euro is required until registration of a new drug. The advent of PET with allied techniques has resulted in a revolutionary change in this respect, as the application of PET in drug development and testing can significantly reduce both molecule-to-drug-time and costs.

During the past decades over a hundred neurotransmitters have been identified in the primate and human brain. Most of the currently used drugs for the treatment of psychiatric and neurological disorders interact with central neurotransmission. Several receptor subtypes, transmitter carriers, and enzymes have proven to be useful targets for drug treatment. Molecular biological techniques have now revealed the existence of several novel receptors for which little or no prior pharmacological or functional data existed. Due to the lack of data on the functional significance of these sites, pharmacologists are now challenged to find the physiological roles of these receptors and identify selective agents and possible therapeutic indications. This is a demanding procedure.

For several neuropsychiatry disorders there is a lack of generally accepted animal models. This is a limitation when exploring the pharmacological significance of new biochemical targets. For instance, the lack of effect in traditional behavioral pharmacology in animals thus not exclude the prospect of a molecule for the treatment of subjectively reported syndromes, such as anxiety or thought disorders, in the more complex human brain. There is an increasing awareness that more efficient and sensitive strategies must be applied in the search for useful medicines. One such strategy is to find methods to test more molecules in early exploratory studies in man. Soon after the first PET scanners have proved to be uniquely useful in medical diagnostics and basic biological research, PET entered the armory of drug research and development. During the past two decades the accumulated experience with PET has clearly shown that the application of the technique is especially useful and promising in the field of neuropsychopharmacology

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